REMARKS:

I. Status of the Claims

Claims 1-38 are pending, with claims 1-10 being withdrawn for being directed to non-elected subject matter, and claims 12, 16, 20, 21, 25, 28, 32, and 34 being withdrawn for being directed to non-elected species. Thus, claims 11, 13-15, 17-19, 22-24, 26, 27, 29-31, 33, and 35-38 are presently under examination. Applicant acknowledges with appreciation the withdrawal of the previous § 102 rejections.

II. 35 USC § 103 Rejections

Reconsideration is respectfully requested of the rejection of claims 11, 13-15, 17-19, 22-24, 26, 27, 29-31, 33, and 35-38 under 35 USC § 103(a) in view of Reed et al. (US 6,727,356) and Nikiforov et al. (US 6,777,184).

Claim 11 is directed to a method for detecting or quantifying a nucleic acid analyte. The method of claim 11 requires providing a nucleic acid probe comprising at least one monomeric LNA moiety and two or more non-identical covalently attached dyes, wherein at least one dye is fluorescent. The method further comprises contacting the nucleic acid analyte with the nucleic acid probe such that the nucleic acid probe hybridizes with the nucleic acid analyte. Lastly, the method comprises measuring the change in fluorescence of the nucleic acid probe that is related to the hybridization of the nucleic acid probe with the nucleic acid analyte.

Claim 24 is also directed to a method for detecting or quantifying a nucleic acid analyte. The method of claim 24 requires providing a pair of nucleic acid probes that differ in their nucleic acid sequences, and collectively comprise at least one monomeric LNA moiety and two or more non-identical covalently attached dyes, wherein at least one dye is fluorescent and wherein each probe comprises at least one of the dyes. The method further comprises contacting the nucleic acid analyte with the pair of nucleic acid probes such that both probes hybridize with adjacent segments of the nucleic acid analyte. Lastly, the method comprises measuring the change in fluorescence of the pair of nucleic acid probes that is related to the hybridization of the pair of nucleic acid probes with the nucleic acid analyte.

The Office states that the only difference between the methods of these two claims is that the method of claim 24 requires a pair of probes while the method of claim 11 requires only a single probe, and accordingly has addressed the two methods together with reference to the requirement of a probe pair. Moreover, in the Office Communication dated May 28, 2009, the Office required several species elections. With regard to the two or more non-identical covalently attached dyes, the Office required an election between 1) dyes comprising a donor dye and an acceptor dye that constitute a FRET system, or 2) dyes comprising a fluorescent dye and a non-fluorescent quencher dye. The Applicant elected *1) in which the probe or pair of probes comprises a donor dye and an acceptor dye*. With regard to the change in fluorescence that is measured in the final step of both processes, the Office required an election between 1) in which the change in fluorescence occurs upon hybridization or 2) in which the change in fluorescence occurs upon hydrolysis of the probe. The Applicant elected *1) in which the change in fluorescence occurs upon hybridization*. Thus, probes comprising a non-fluorescent quencher dye and probes whose detection is based upon hydrolysis (such as, *e.g.*, Taqman probes) were withdrawn from consideration by virtue of the restriction requirement.

Despite the mandated species restrictions and Applicants' elections of record, the Office is now citing examples of Taqman probes in Reed et al. (S*ee* Office action dated 3/17/10 at page 3, paragraphs 1-3 and 5-8 where it is stated "see col. 5 lines 16-32 where SNP analysis using Taqman is referenced"). Reed et al. disclose numerous types of probes, but as correctly noted by the Office, Reed et al. fail to disclose probes comprising at least one monomeric LNA moiety.

The Office states that it would have been "obvious to one of ordinary skill in the art at the time of the invention to use the LNA moiety, as taught by Nikiforov et al., with the probes as taught by Reed et al. (*See* Office action dated 3/17/10, at page 4). It is respectfully submitted that the disclosure of Nikiforov et al. fails to provide sufficient guidance *to predictably yield* probes comprising LNA(s) as required in either claim 11 or claim 24. According to M.P.E.P. 2121, a reference must be enabled to be considered as prior art in an obviousness rejection. It is respectfully submitted that Nikiforov et al.

is not enabled with regard to probes comprising LNA(s). For example, Nikiforov et al. fail to describe any specific probes comprising LNA(s) or provide any working examples of probes comprising LNA(s). Rather, the term LNA always appears within a list of possible entities. Examples include the following:

> "Thus, probes (e.g., PNAs, DNAs, LNAs, RNAs or other nucleic acids, or even other nucleic acid binding moieties) can be labeled with . . . ," (at column 3, lines 48-51).
>
> "Common nucleic acids, as used herein, include DNAs, RNAs, LNAs, PNAs, and many modified forms of these molecules . . . ," (at column 7, lines 27-29).
>
> ". . . a probe nucleic acid comprising a PNA (or a DNA, LNA, or RNA, etc.) comprising a rhodamine label," (at column 7, lines 40-42).
>
> " . . . comprises one or more of: DNA, RNA, LNA, a DNA analog, an RNA analog or a PNA," (see claims 7 and 38).

Simply put, this reference provides no guidance with regard to the number of LNA(s) in a probe, the position of the LNA(s) in a probe, the length of a probe comprising LNA(s), etc. Given the disclosure of Nikiforov et al., a person of ordinary skill in the art *would not have been able to arrive at the probes required in the claimed methods with a reasonable expectation of success*. In particular, although the Office states that Nikiforov et al. disclose probes in which "the LNA moiety is complementary to the opposing SNP site" (*see* Office action dated 3/17/10, at page 4, paragraph 8), this is not correct. Nowhere does Nikiforov et al. describe the location of a LNA moiety in a probe.

Applicant respectfully submits that incorporating LNAs into nucleic acid probes was not obvious at the time of the invention, and incorporating LNAs into nucleic acid probes was not a trivial undertaking. Rather, the design and preparation of probes comprising LNA(s) required significant trial and error experimentation with *no predictable results*. For example, at the time of the invention it was unknown whether LNA(s) should be located in internal position(s), at penultimate position(s), or at terminal position(s) of a nucleic acid probe. Similarly, it was unknown whether one LNA was optimal, whether increasing numbers of LNAs increased probe specificity, or whether

the probe should be composed of all LNAs. As demonstrated in the Examples 4 and 5 of the pending application, Applicant discovered for the first time that LNA moieties could be located in any of several interior positions. Additionally, it was discovered that multiple LNAs could be dispersed throughout a probe (*see*, *e.g.*, probe pair 2 in Tables 1, 2, and FIG. 1B; and probe pair 7 in Tables 3, 4, and FIG. 3B) or multiple LNAs could be clustered in a probe (*see*, *e.g.*, probe pair 3 in Tables 1, 2, and FIG. 1C; and probe pair 8 in Tables 3, 4, and FIG. 3C). Moreover, Applicant discovered through trial and error experimentation that probes with increasing numbers of LNAs could be made shorter in length, while still retaining significant specificity and discrimination ability (*see*, *e.g.*, probe pair 5 in Tables 1, 2, and FIG. 1E; and probe pair 10 in Tables 3, 4, and FIG. 3E). Additionally, considerable research effort was required to determine conditions under which oligonucleotides comprising LNAs could be efficiently synthesized using "routine" phosphoramidite procedures. Thus, the modification of the probes of Reed et al. to contain LNA moieties of Nikiforov et al. as proposed by the Office was not obvious because the modification was not a matter of routine skill, nor were the results predictable. Neither Nikiforov et al. nor knowledge generally available to those of skill in the art provided sufficient guidance to arrive at the probes required in claims 11 or 24 with a reasonable expectation of success.

In summary, the cited references do not disclose or suggest all of the limitations of the LNA-containing probes required in the method of either claim 11 or claim 24. Additionally, neither the cited references nor commonly available knowledge provided sufficient guidance to arrive at the LNA-containing probes used in the method of either claim 11 or claim 24 with a reasonable expectation of success. Accordingly, it is respectfully submitted that claim 11 is not obvious in view of Reed et al. and Nikiforov et al. Claims 13-15, 17-19, and 22-23, which depend from and incorporate all the limitations of claim 11, likewise are not rendered obvious by the cited art for the same reasons stated above with respect to claim 11. Furthermore, Applicant respectfully submits that claim 24 is not obvious in view of the cited art. Claims 26, 27, 29-31, 33, and 35-38, which depend from and incorporate all the limitation of claim 24, likewise are

not obvious in view of Reed et al. and Nikiforov et al. for the same reasons stated above with respect to claim 24.

In view of the above, Applicant respectfully requests withdrawal of the rejection of claims 11, 13-15, 17-19, 22-24, 26, 27, 29-31, 33, and 35-38 under 35 USC § 103(a) in view of Reed et al. and Nikiforov et al.

III. Conclusions

In light of the foregoing, the Applicant requests withdrawal of the claim rejections and solicits an allowance of all pending claims. The Examiner is invited to contact the undersigned practitioner should any issues remain unresolved.

Respectfully submitted,
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